Synthesis of Novel Phenylnaphthyl Phosphines and their Applications to Pd-Catalyzed Intramolecular Amidation

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This paper is dedicated to the memory of the late Professor Kiyoshi Tanaka who passed away December 8, 2004.

Abstract: Novel phenylnaphthyl phosphines were prepared and applied to the Pd-catalyzed intramolecular amidation. Both ligands gave good to excellent yields in the synthesis of five-, six-, and seven-membered rings from halo-amides and carbamates.

Key words: phenylnaphthyl phosphine, Pd catalysis, C–N bond formation, intramolecular amidation, Suzuki–Miyaura cross-coupling

Transition-metal catalyzed carbon–heteroatom bond formation is a powerful tool for the synthesis of highly complex molecules.[1] Furthermore, transition metal catalyzed reactions are compatible with many functional groups, which enables the total synthesis of nitrogen-containing natural products[2] and the construction of heterocycles in drug development.[3]

Since Buchwald reported the pioneering Pd-catalyzed C–N bond formation,[4] biphenyl phosphines **1**[4a] and **2**[4b] are recognized as effective ligands for these reactions (Figure 1). On the other hand, binaphthyl phosphines, BINAP **3**,[5] and MOP **4**,[6] have also played a key role in the development of efficient Pd-mediated catalytic systems.

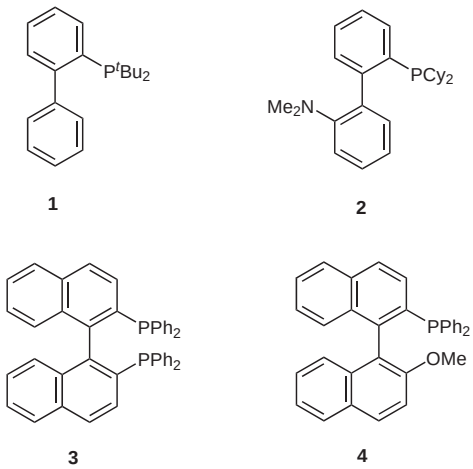

Figure 1 Biphenyl and binaphthyl phosphines used in Pd-catalyzed C–N bond formation.

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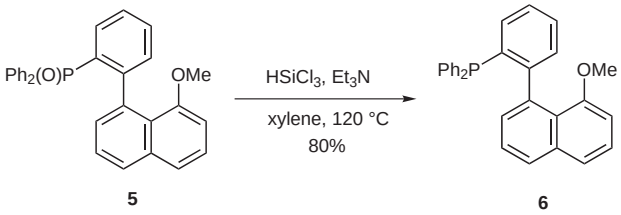
However, even with these well-designed ligands, unsatisfactory results were sometimes observed since the efficiency of such reactions strongly depends on the fine electronic and structural properties of the ligands, therefore, novel phosphine ligands are required.

Recently, we reported the efficient preparation of 1-methoxy-8-phenylnaphthalene derivatives and the preliminary investigation of their optical behavior.[7,8] We envision that phenylnaphthyl phosphine derivatives **6** and **11**, which are readily prepared by our method, would be excellent ligands for Pd-mediated C–N bond formation. Herein, the preparation of novel phenylnaphthyl phosphines **6** and **11** and their applications to Pd-catalyzed intramolecular amidations are described.

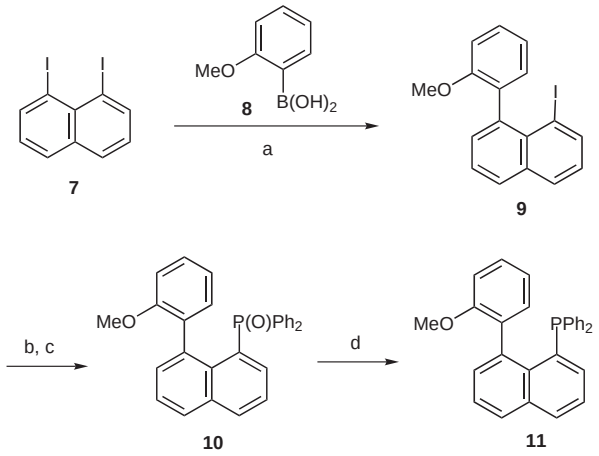
As shown in Scheme 1, phosphine **6** was prepared in 80% yield from **5**[7] by treatment with $HSiCl_3$.[9] Once phosphine **6** was synthesized, we focused our attention on the analogous phosphine **11**, which should exhibits different electronic and steric properties to **6** (Scheme 2).



Scheme 1 Preparation of phenylnaphthyl phosphine **6**.

We selected 1,8-diiodonathphalene (**7**), which has sufficient reactivity to undergo cross-coupling reactions, as the starting material for **11**. Upon treating **7** and 2-methoxyphenylboronic acid (**8**) with 5.0 mol% of $Pd(PPh_3)_4$ and Cs_2CO_3, the selective Suzuki–Miyaura cross-coupling[10] proceeded smoothly to afford biaryl iodide **9** in good yield. Successive treatment with *n*-BuLi and diphenylphosphinic chloride afforded phosphine oxide **10** in 62% yield. Finally, $HSiCl_3$ reduction of **10** provided the desired phosphine **11**.[11]

The potential of **6** and **11** as ligands was evaluated by the Pd-mediated intramolecular amidation of aryl bromide **12**, which was reported by Buchwald.[12] As shown in Table 1, the cyclization was successful when phosphine **6** was employed. Although the reaction did not proceed



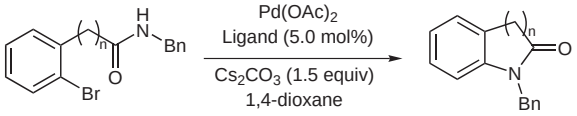
Scheme 2 Preparation of phenylnaphthyl phosphine **11**. *Reagents and conditions*: a) $Pd(PPh_3)_4$ (5.0 mol%), Cs_2CO_3, toluene–EtOH–H_2O (3:2:2), 100 °C, 66%; b) *n*-BuLi, Et_2O, –78 °C; c) $Ph_2P(O)Cl$, Et_2O, –78 to 50 °C, 62% (two steps); d) $HSiCl_3$, Et_3N, xylene, 120 °C, 34%.

smoothly using Buchwald conditions[12a] (Table 1, entry 1), using Cs_2CO_3 instead of K_2CO_3 improves the yield of **13** to 44% (Table 1, entry 2). Furthermore, changing the solvent from toluene to 1,4-dioxane results in an 80% yield of **13** after 3.5 hours (Table 1, entry 3). The combination of 5.0 mol% **6** and 6.0 mol% $Pd(OAc)_2$ gave the best result (Table 1, entry 4).[13] These results prove the outstanding ability of **6** as a ligand giving a reaction about ten times shorter than that previously reported.[14]

Although **11** possesses similar functional groups to **6**, cyclization did not occur (Table 1, entry 5).[16] This dramatic difference in the reactivity might be due to the steric bulkiness of the phenyl moiety of **11**, in a 1,8-relationship to the diphenylphosphino group on the naphthyl ring. Such a steric effect could make oxidative addition of the Pd(0)-**11** complex to aryl bromide **12** difficult. We also looked at the reactivity of ligand **14**,[15] which is similar to **11** in that both lack a methoxy group on the naphthyl ring, however ligand **14** provided **13** in 45% yield (Table 1, entry 6). This difference in reactivity suggests that the methoxy group plays an important role in the superior catalytic activity of the Pd(0)-**6** complex. The electron donating ability of the methoxy group might facilitate the π-coordination of the naphthyl moiety to Pd(0) and lead to stabilization of the catalytically active low-coordinate Pd species.[17]

Both ligands **6** and **11** were then applied to the synthesis of six- and seven-membered rings (Table 2). Lactam construction proceeded smoothly using ligands **6**, **11**, and **14**, providing **17** in excellent yields (Table 2, entries 1–3). It is noteworthy that ligand **11**, which was ineffective for the formation of a five-membered ring (Table 1, entry 5), gave an excellent result here.

Table 2 Cyclization of Amides **15** and **16**



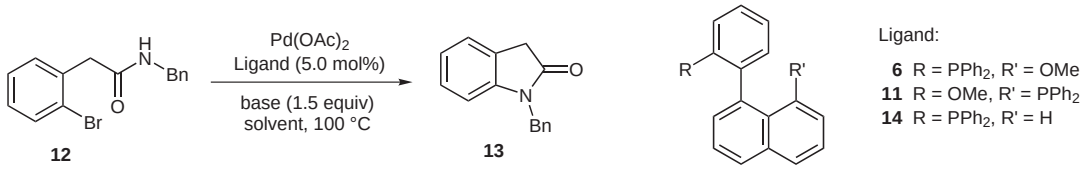
15: n = 2
16: n = 3

17: n = 2
18: n = 3

Entry	n	Pd (mol%)	Ligand	Conditions	Yield (%)
1	2	6.0	**6**	100 °C, 3.5 h	91
2	2	6.0	**11**	100 °C, 3.5 h	85
3	2	6.0	**14**	100 °C, 3.5 h	95
4	3	6.0	**6**	100 °C, 3.5 h	7
5	3	3.0	**6**	reflux, 48 h	51
6	3	3.0	**11**	reflux, 48 h	trace
7	3	3.0	**14**	reflux, 48 h	34

Ligand **6** resulted in a seven-membered lactam, and although only 3.0 mol% of $Pd(OAc)_2$ was required, a longer reaction time under reflux conditions was necessary (Table 2, entry 5). The reactivities of ligands **6**, **11**, and **14** in this reaction were similar to those observed in the formation of five-membered rings (Table 1, entries 4–6).[18]

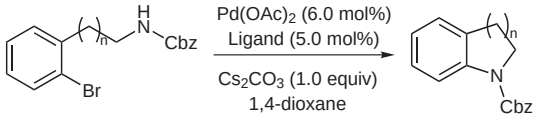
Table 1 Five-Membered Ring Formation of Amide **12**



Entry	Pd (mol%)	Ligand	Base	Solvent	Time (h)	Yield (%)
1	3.3	**6**	K_2CO_3	Toluene	36	11
2	3.0	**6**	Cs_2CO_3	Toluene	3.5	44
3	3.0	**6**	Cs_2CO_3	1,4-Dioxane	3.5	80
4	6.0	**6**	Cs_2CO_3	1,4-Dioxane	3.5	85
5	6.0	**11**	Cs_2CO_3	1,4-Dioxane	3.5	trace
6	6.0	**14**	Cs_2CO_3	1,4-Dioxane	3.5	45

To construct indoline and quinoline derivatives, we undertook the cyclization of **19** and **20**. As shown in Table 3, cyclization was successful with ligands **6** and **11**.

Table 3 Cyclization of Carbamate Derivatives **19** and **20**



19: n = 1
20: n = 2

21: n = 1
22: n = 2

Entry	n	Ligand	Yield (%)
1	1	**6**	69
2	1	**11**	51
3	2	**6**	89
4	2	**11**	79

In conclusion, our newly prepared phenylnaphthyl phosphines **6** and **11** have sufficient activity as ligands for Pd-catalyzed intramolecular amidations. These ligands are easy to use and stable under several conditions.

Further tuning of the ligand structure taking advantage of the methoxy group, as well as applications of **6** and **11** to other transition-metal catalyzed reactions are currently underway.

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(6) For a review on MOP, see: Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.

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(8) Our group has used the structurally related optically active 8,8′-disubstituted 1,1′-binaphthyls as chiral modifiers. For examples, see: (a) Fuji, K.; Ohnishi, H.; Moriyama, S.; Tanaka, K.; Kawabata, T.; Tsubaki, K. *Synlett* **2000**, 351. (b) Tanaka, K.; Nuruzzaman, M.; Yoshida, M.; Asakawa, N.; Yang, X.-S.; Tsubaki, K.; Fuji, K. *Chem. Pharm. Bull.* **1999**, *47*, 1053. (c) Fuji, K.; Yang, X.-S.; Ohnishi, H.; Hao, X.-J.; Obata, Y.; Tanaka, K. *Tetrahedron: Asymmetry* **1999**, *10*, 3243. (d) Tanaka, K.; Asakawa, N.; Nuruzzaman, M.; Fuji, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3637.

(9) The ligand **6** could be purified by column chromatography under atmospheric conditions. Spectral data of **6**: ^{1}H NMR: δ = 3.37 (s, 3 H), 6.67–6.65 (m, 1 H), 6.86 (dd, *J* = 0.8, 7.0 Hz, 1 H), 7.16–7.11 (m, 5 H), 7.27–7.21 (m, 9 H), 7.37–7.31 (m, 2 H), 7.74–7.44 (m, 1 H), 7.74 (dd, *J* = 0.8, 8.0 Hz, 1 H). MS (FAB): *m*/*z* = 419 (M + H)$^+$. HRMS: *m*/*z* calcd for $C_{29}H_{24}OP$ (M + H)$^+$, 419.1564; found, 419.1531.

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(11) Spectral data of **11**: ^{1}H NMR: δ = 3.48 (s, 3 H), 6.65–6.60 (m, 1 H), 6.83–6.70 (m, 4 H), 7.30–7.00 (m, 13 H), 7.50–7.45 (m, 1 H), 7.88 (d, *J* = 7.9 Hz, 2 H). MS (FAB): *m*/*z* = 419 (M + H)$^+$. HRMS: *m*/*z* calcd for $C_{29}H_{24}OP$ (M + H)$^+$, 419.1564; found, 419.1524.

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(13) **Intramolecular Amidations; General Procedure**
To a mixture of **6** (9.8 mg, 23 μmol) and $Pd(OAc)_2$ (6.3 mg, 28 μmol) in 1,4-dioxane (3.0 mL) was added **12** (142 mg, 0.47 mmol) and Cs_2CO_3 (228 mg, 0.70 mmol) at r.t. The reaction was stirred at 100 °C for 3.5 h, EtOAc and H_2O were added, and the resulting mixture was filtered through a pad of Celite. The organic layer was separated, washed with brine, dried over $MgSO_4$, and then evaporated to give a residue, which was purified by column chromatography (SiO_2; hexane–EtOAc, 3:2) to afford **13** (88 mg, 85%).

(14) In a previous report, the cyclization of **12** was conducted with $Pd(OAc)_2$ (3.3 mol%), (*dl*)-MOP (5.0 mol%), and K_2CO_3 (1.4 equiv) in toluene at 100 °C for 36 h to give **13** in 82%; see, ref. 12a.

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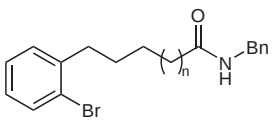
(16) The starting material **12** was recovered in 72% yield. No reductive dehalogenation of **12** as a side reaction was observed.

(17) Both η^1- and η^2-coordinations of arenes to Pd(0) were previously proposed as plausible explanations for the excellent properties of electron-rich biaryl phosphines: (a) For η^1-coordination, see: Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7816. (b) For η^2-coordination, see: Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

(18) Attempts to synthesize the eight-, nine-, and ten-membered lactams using **23**, **24**, and **25** as the starting materials, respectively, were unsuccessful (Figure 2).
In every case only the starting materials were recovered.



23: n = 1
24: n = 2
25: n = 3

Figure 2 Substrates for eight- to ten-membered lactam formation.